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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/351,778	07/12/1999	WILLIAM S. M. WOLD	16153-7775	1203

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EXAMINER
PRIEBE, SCOTT DAVID

ART UNIT	PAPER NUMBER
1632	26

DATE MAILED: 03/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/351,778	Wold et al.
Examiner	**Art Unit**
Scott D. Priebe, Ph.D.	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jan 6, 2003*.

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1, 2, and 4-59* is/are pending in the application.

4a) Of the above, claim(s) *6-9, 16-19, 23, and 25-31* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 2, 4, 10-14, 20-22, 24, and 32-59* is/are rejected.

7) ☒ Claim(s) *5 and 15* is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☒ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The amendment filed 1/6/03 has been entered. Claims 33-59 have been added.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restriction

Claims 6-9, 16-19, 23 and 25-31 remain withdrawn and new claims 28-31 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made without traverse in Paper No. 9.

Specification

The disclosure is objected to because of the following informalities: Table 1 lists a deletion of "Ad5 bp 27858-2760" for KD1, GZ1 and KD1-SPB. This appears to be a mistake with respect to "2760". Correction of this mistake should include no new matter; Applicant must provide evidence that the correction does not introduce new matter.

Appropriate correction is required.

Claim Objections

Claims 56-58 are objected to because of the following informalities: Claims 56-58 depend from dependent claim 38, but are separated from claim 38 by dependent claims, e.g. claim 55, which does not also depend from claim 38.

A series of singular dependent claims is permissible in which a dependent claim refers to a preceding claim which, in turn, refers to another preceding claim. A claim which depends from a dependent claim should not be separated by any claim which does not also depend from said dependent claim. It should be kept in mind that a dependent claim may refer to any preceding independent claim. In general, applicant's sequence will not be changed. See MPEP § 608.01(n).

Appropriate correction is required.

Claim Rejections - 35 USC § 112

Claims 40, 45-55 and 59 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 40 is directed to the adenovirus of claim 1 wherein the 6.7K or 12.5K protein coding sequence or both is deleted. This claim embraces species wherein the gp 19K, RID and 14.7K proteins are functional, or where the coding sequence of one of the 6.7K or 12.5K protein

coding sequence is deleted. Applicant has not pointed to where the specification supports this broadly claimed subject matter. The specification (page 15, lines 12-15) teaches deletion of both the 6.7K and 12.5K protein coding sequences in addition to one or more of the gp 19K, RID and 14.7K protein coding sequences. It does not teach deletion of the 6.7K or 12.5K coding sequence alone, nor does it teach deletion of both without deletion of one or more of the gp 19K, RID and 14.7K protein coding sequences.

Claims 45, 51 and their dependent claims are directed to adenovirus vectors which lack expression of one or more E3 proteins and comprise "a gene that encodes ADP". As written, these claims do not require the adenovirus to be replication competent in neoplastic cells or any other cells, i.e. the adenovirus may be replication defective. The term gene is not defined in the specification, but at page 13, lines 2-8 the term "gene" is used to mean coding sequence, and not including sequences necessary to express the protein since the gene is to be linked to sequences providing those functions. Thus, recitation of "gene" only means that the ADP coding sequence be present, and not necessarily linked to sequences required for its expression. Consequently, claims 45 and 51 do not require the ADP to be expressed, much less overexpressed.

Applicant has not pointed to where the specification supports this subject matter, which is their burden, MPEP 714.02 (last sentence of 3rd para. from end) and 2163.06(l) (last sentence). Rather, Applicant merely asserts that it is supported. These claims are much broader than the adenovirus vector invention described in the specification repeatedly as adenovirus vectors which are replication competent in neoplastic cells and overexpress ADP (see for example page 5, lines

16-31). There is no clear support in the specification for the broader invention now being claimed which would embrace adenovirus which are replication-defective in all but packaging cells or replication competent in some natural cells but not neoplastic cells; adenovirus which comprise the ADP coding sequence but either do not express ADP or do not overexpress ADP.

Claims 1, 2, 4, 10-14, 21, 22, 24, and 32-44 are rejected under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter which applicant(s) regard as their invention. Evidence that claims 1, 2, 4, 10-14, 21, 22, 24, and 32-44 fail(s) to correspond in scope with that which applicant(s) regard as the invention can be found in Paper No. 26 filed 1/6/03. In Paper No. 26, applicant has stated that dl309 and CN751 while meeting the structural criteria by which an adenovirus which overexpresses ADP may be recognized or made, removal of a splicing signal, these two adenovirus do not overexpress ADP, and this statement indicates that the invention is different from what is defined in the claim(s) because the specification explicitly states:

> In general, any type of deletion in the E3 region that removes a splice site for any E3 pre-mRNAs will lead to overexpression of the mRNA for ADP, inasmuch as more of the E3 pre-mRNA molecules will be processed into the mRNA for ADP.

In the response filed 6/11/01, page 5, Applicants affirmed this description of their invention, concluding that one of skill in the art with the specification in hand "would recognize that overexpression, as herein defined, means the expression of ADP *beyond* what is normally expressed, both early and late in the infection cycle." In Paper No. 26, as evidence that dl309

does not overexpress ADP, comparison is made between dl309 and KD1 or KD3. While it is clear that KD1 and KD3 overexpress ADP at early stages of infection, the evidence that ADP is overexpressed by KD1 or KD3 when all stages of infection are considered is equivocal (see e.g. instant Figure 2). It would be more accurate to say that ADP expression in KD1 is temporally shifted (to earlier in the viral cycle), evidence that levels of ADP in KD1 infected cells by the end of a viral generation are higher as compared to dl309. Considering that KD1 and KD3 begin to accumulate ADP earlier in infection (at 24 hr p.i.), in order for dl309 to have achieved a comparable level of ADP by later in infection, ADP expression must have been higher after 24 hr p.i. When the course of the life cycle is considered in determining ADP expression level, dl309 produces an amount of ADP which cannot be reliably distinguished from that produced in KD1 or KD3. See instant Fig. 2. Also, Doranin et al. (J. Virol. 74 (13): 6147-6155, 2000) stated (page 6150, col. 1) that the level of ADP expressed in dividing A549 cells infected with KD1 or KD3 was "perhaps a little more than *dl309*" (emphasis added). By comparing dl309 to KD1 or KD3, Applicant appears to be equating general "overexpression" as recited in the claims with overexpression at early stages of infection, contrary to the definition in the specification as indicated in the response filed 6/11/01.

Claim Rejections - 35 USC § 102 & 103

Claims 1, 2, 4, 10-12, 32, 33, 35, 40, 45-49, and 51 are rejected under 35 U.S.C. 102(b) as being anticipated by Tollefson et al. (Virol. 220: 152-162, 1996) as evidenced by the Declaration filed 1/6/03 for claims 1, 2, 4, 10-12, 32, 33, 35, and 40.

Tollefson discloses a series of adenovirus vectors which express ADP and which have deletions in various E3 open reading frames, resulting in loss of expression of the proteins encoded thereby (Fig. 1A). At least one of these, dl753, overexpresses the ADP protein according to the Declaration. Fig. 2 shows a method of using dl753 for promoting death of A549 cells, which are neoplastic. At least one of these, dl722, removes the splicing site in the E3 pre-mRNA at nucleotide 372 in Fig. 1A, according to the specification at page 12, the removal of this splice site should lead to overexpression of ADP.

Claims 1, 2, 4, 10-12 and 32 remain rejected and claims 33, 35-37, 39-41, 45, 47-47, 51, and 59.are rejected under 35 U.S.C. 102(b) as being anticipated by Tollefson et al. (J. Virol., 70(4):2296-2306, 4/96), as evidenced by Bett et al. (Virus Res. 39: 75-82, 1995) for the reasons of record set forth in the Office action of 7/5/02.

Applicant's arguments filed 1/6/03 have been fully considered but they are not persuasive. Applicant states that Tollefson et al. does not disclose that dl309 is capable of overexpressing ADP, and that the conclusion that dl309 does overexpress ADP is based upon the teaching in the specification (page 12, lines 33-35:

> In general, any type of deletion in the E3 region that removes a splice site for any E3 pre-mRNAs will lead to overexpression of the mRNA for ADP, inasmuch as more of the E3 pre-mRNA molecules will be processed into the mRNA for ADP.

Applicant states that while they believe this statement to be generally true, the evidence in Tollefson suggests that dl309 produces normal, wild type levels of ADP based upon plaque size. Further, the specification teaches that dl309 has wild-type expression of ADP, pointing to Figures 2 and 5. Applicant characterizes Figure 2 as showing, for dl309-infected A549 cells, no expression of ADP at 24 hours p.i., and "very little" expression at 36 hours p.i. relative to KD and GZ vectors. Applicant also interprets results of cell spread assays (Fig. 5) as meaning higher ADP expression occurs in KD and GZ vectors. Based upon these arguments, Applicant concludes that no credible evidence has bee provided that dl309 overexpresses ADP.

In response, the claims do not specify the criteria upon which overexpression of ADP is to be evaluated to determine the metes and bounds of the claims, i.e. there is no standard against which overexpression is to be measured. Also, any amount of overexpression is overexpression, even if as little as a single ADP molecule. Comparison to KD or GZ vectors is not a measure of whether a different vector, e.g. dl309, overexpresses ADP. Also, there is no restriction on when ADP expression is to be compared, e.g. early vs. late in the infection cycle. Finally, characteristics which do not directly and unequivocally relate to ADP expression, e.g. plaque size, cell spread, etc. are irrelevant. Whether or not the results of these assays may correlate with ADP expression, no direct quantitative relationships have been established that would allow one to assess ADP expression levels based upon such indirect assays.

The final version of Fig. 2 filed 08/01/00 shows that KD1 and KD3 produced little ADP at 24 hr p.i. compared to at 36 hr p.i., while dl309 shows no detectable ADP at 24 hours p.i. and substantially the same level of ADP at 36 hr p.i. as seen for KD1 and KD3. The "gel spots" of ADP in the dl309 36 hr lane cover less area than those for the KD1 and KD3, but are more intense; it appears that the ADP migrated in a tighter band in the dl309 lanes as compared to the KD1 and KD3 lanes. No quantitative measurement of ADP levels is provided in the specification. In describing results of a similar experiment, Doranin et al. (J. Virol. 74 (13): 6147-6155, 2000) stated (page 6150, col. 1) that the level of ADP expressed in dividing A549 cells infected with KD1 or KD3 was "perhaps a little more than *dl309*" (emphasis added); i.e. it was equivocal whether it was more. Consequently, when measured at 36 hr p.i. there is no evidence that KD1 and KD3 infected cells have accumulated any more ADP than dl309 infected cells. In both cases the ADP levels were qualitatively determined by immunoblotting, which means that the ADP observed is that accumulated in the cell culture at 36 hr p.i., this does not measure current production rates or levels at the 36 hr p.i. time point, such as would be measured by a pulse-chase assay. KD1 and KD3 infected cells clearly produce more ADP at earlier time points than do dl309 infected cells, i.e. by 36 hr p.i. KD1 and KD3 infected cells have accumulated more ADP from earlier times than has dl309. These results suggest that new production of ADP is higher at later time points in dl309 infected cells than for KD1 or KD3 infected cells, i.e. at 36 hr p.i. dl309 overexpressed ADP relative to KD1 and KD3, since the accumulated level of ADP expressed from dl309 by 36 hr p.i. is equal to that of KD1 and KD3.

In addition, Doranin disclosed that quiescent cells infected with KD1 or KD3 show cytopathic effects much later than does dl309 (17 d p.i. vs. 8 d p.i.). If, as Applicant alleges, rate of plaque formation (which results from cytopathic effects on infected cells) is an indication of ADP expression, then one would conclude that in quiescent cells dl309 expresses more ADP than does KD1 or KD3. The claims set no limits on how overexpression is to be determined. Consequently, if KD1 and KD3 "overexpress" ADP, and the specification clearly teaches that they do, so also does dl309.

Finally, there is credible evidence that dl309 overexpresses ADP. First, the specification clearly and explicitly teaches that removal of any splice site from the E3 pre-mRNA results in ADP overexpression. Since dl309 comprises a deletion that would remove such a splice site, then by this criterion, set forth in the specification, dl309 must overexpress ADP. Second, the specification teaches that KD1 and KD3 overexpress ADP, and comparison of cumulative ADP expression at 36 hr p.i. shows comparable levels of ADP for KD1, KD3 and dl309. Therefore, based upon comparison to an adenovirus which is taught overexpresses ADP, dl309 also overexpresses ADP. The claims do not require that overexpression be determined by measuring expression at 24 hr p.i. or any other time that KD1 or KD3 is producing more ADP than would dl309, i.e. a determination of whether an adenovirus overexpresses ADP may be made at 36 hr p.i. Also, while the skilled artisan may view dl309 as comparable to wild type in its replication, it clearly is not wild type. While the level and temporal pattern of ADP expression from dl309 may be closer to wild type than KD1 or KD3, no quantitative evidence has been presented that dl309

expresses the same level of ADP throughout the viral infection cycle. Even if dl309 expresses as little as a single molecule of ADP beyond that expressed by Ad5, for example, by the end of an infection cycle, it would meet the claim limitation.

Applicants' arguments do not apply to new claims 45-55 and 59, which do not require any expression of ADP, much less overexpression.

Claims 1, 2, 4 and 10-13 remain rejected and claims 33-59 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by Henderson et al. (U.S. 6,197,293, filed 3/02/98) for the reasons of record set forth in the Office action of 3/15/01.

Claims 1, 2, 4 and 10-13 remain rejected and claims 33-59 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by Little et al. (U.S. 6,254,862, filed 3/02/98) for the reasons of record set forth in the Office action of 8/24/01.

Claims 13 and 20-22 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Henderson et al. (U.S. 6,197,293) as applied to claims 1, 2, 4, 10-13, and 33-59 above in view of Freytag et al. (Hum. Gene Ther., 9:1323-1333, 6/10/98) for the reasons of record set forth in the Office action of 3/15/01.

Claims 13 and 20-22 remain are rejected under 35 U.S.C. 103(a) as being unpatentable over Little et al. (U.S. 6,254,862) as applied to claims 1, 2, 4, 10-13, and 33-59 above in view of Freytag et al. (Hum. Gene Ther., 9:1323-1333, 6/10/98).

Applicant's arguments filed 1/6/03 have been fully considered but they are not persuasive. Applicant presents two lines of argument: first, adenovirus CN751 does not lead to overexpression of ADP, and second, Applicant conceived of the instant invention prior to the effective dates of Henderson or Little, and diligently reduced it to practice subsequent to conception.

With respect to whether CN751 meets the claim limitations. First, Applicants have admitted in their response filed 1/10/02 (page 7) that both Little and Henderson "disclose a recombinant adenoviral vector that is replication-restricted to neoplastic cells and which overexpresses an adenoviral death protein." The Office concurs with this statement based upon the specification. CN751 (Henderson, Ex. 4; Little, Ex. 5) comprises no E3 coding sequence other than for ADP, and lacks most, if not all, of the same splice sites missing from KD1 and KD3. CN751 comprises the E3 deletion of BHG11 into which were inserted Ad2 nucleotides 28287-28622 (untranslated Y leader) fused to Ad2 nucleotides 29195-29872 (Ad2 ADP coding sequence). Bett et al. (Proc. Natl. Acad. Sci. 91: 8802-8806, 1994, at page 8803, col. 2) discloses that BHG11 has a deletion of Ad5 E3 nucleotides 27,865-30,995. Consequently, CN751 lacks all Ad5 E3 coding sequence and has the Ad2 ADP coding sequence. The location and extent of the deletions in CN751 is very similar to that of KD1. Henderson (col. 27, lines 43-63) and Little (col. 21, line 63 to col. 22, line 29) both teach that the Y leader segment may be omitted. The resulting adenovirus would lack even more E3 sequences than does KD1 or KD3. Since CN751

comprise deletions that would remove E3 splice sites, then by this criterion, set forth in the specification, CN751 must overexpress ADP.

Finally, characteristics, e.g. plaque size, cell spread, cytotoxicity etc., which do not directly and unequivocally relate to ADP expression in a known quantitative fashion are irrelevant. Whether or not the results of these assays may correlate with ADP expression, no direct quantitative relationships have been established that would allow one to assess ADP expression levels based upon such indirect assays. Direct comparison of ADP expression levels would be required to show that CN751 did not overproduce ADP. Applicant should be aware that should CN751 (or dl309) prove not to overexpress ADP, such evidence would call into question the sufficiency of the disclosure to adequately describe and enable the claimed generic invention. The teaching that removal of splice sites would lead to ADP overexpression would be cast in serious doubt, and the specification provides no other guidance on manipulating the E3 region beyond the specific E3 mutations of KD1 and KD3.

The declaration filed on 1/6/03 under 37 CFR 1.131 has been considered but is ineffective to overcome the Henderson or Little references. The evidence submitted is insufficient to establish a conception of the invention prior to the effective date of the Henderson or Little references. While conception is the mental part of the inventive act, it must be capable of proof, such as by demonstrative evidence or by a complete disclosure to another. Conception is more than a vague idea of how to solve a problem. The requisite means themselves and their

interaction must also be comprehended. See *Mergenthaler v. Scudder*, 1897 C.D. 724, 81 O.G. 1417 (D.C. Cir. 1897).

The rejected claims are directed to a generic invention embracing any adenovirus construction that results in overexpression of ADP, not just deletions of sequences from E3, see page 12, line 32 to page 13, line 8). The declaration provides no evidence of when means other than deletions in E3 were conceived. The declaration establishes that KD1 was conceived before the effective date of the patents. However, the claimed invention is an adenovirus vector that overexpresses ADP protein, and is not limited to adenovirus which possess the E3 region of KD1 as the means for overexpressing ADP. It is well established that conception of a single species cannot support a genus where the genus is large or the subject matter is unpredictable (MPEP 715.03). The only teaching in the specification relating to modifications to the E3 region as a means for overexpressing ADP is to remove a splice site for any E3 pre-mRNA. Both dl309 and CN751 meet this criterion, yet Applicant argues that neither overexpresses ADP. Consequently, it is clear that one cannot predict which E3 sequence(s) can be removed to cause overexpression of ADP. So the issue is not when KD1 was conceived and actually reduced to practice, but when the generic invention was conceived and reduced to practice. The Declaration and its attendant materials do not provide evidence of when Applicant conceived of the generic invention nor when Applicant conceived that KD1 or other vectors such as KD2 and KD3 planned prior to the effective date of the patent would be embraced by the generic invention now claimed. As

indicated on pages 7 and 8 of the declaration, it was not until after 4/18/97 that Applicants were aware that KD1 "overexpresses ADP", which is after the effective dates of Henderson and Little.

Contrary to Applicants' assertion in paragraph 5 (last bullet) of the declaration, there is no suggestion in Exhibit B, page 7, that general overexpression of ADP was being contemplated, as opposed to overexpression during early stages of infection. In the response filed 6/11/01, Applicant clearly indicates that one of skill in the art with the specification in hand "would recognize that overexpression, as herein defined, means the expression of ADP *beyond* what is normally expressed, both early and late in the infection cycle." Exhibit B says nothing about overexpression late in the infection cycle. There is no evidence in Exhibit B that Applicants had conceived of or comprehended the requisite means and their interactions given that the proposal was to carry out research to determine if "11.6K overexpressed during early stages of infection can promote cell death" (emphasis added), much less in the late stages as well. Nor is there any mention that removal of E3 splice sites would facilitate ADP overexpression, as asserted in the declaration. Section C.1.b, page 4 of Exhibit B is describing adenoviral vectors in general, not the KD/GZ class of vectors as asserted. Also, page 5 of Exhibit B states "the vector should probably be defective" of replication. The claimed invention is to an adenovirus that replicates in neoplastic cells, not a replication defective adenovirus. This distinction is important since it is clear from Exhibit B that adenovirus is proposed only as one platform for delivering ADP as the therapeutic agent, not as in the instant invention where a replication competent adenovirus itself is the therapeutic agent, and the overexpression of ADP is to improve its cytotoxicity in

neoplastic cells. Exhibit B does not contain any description of what adenoviral structures would result in "11.6K overexpressed during early stages of infection," especially since this proposes to find that out. In addition, no evidence been provided establishing a nexus between Exhibit B, and any of the experiments related to exhibits C-L.

The relationship between Exhibit A and Exhibits B-L or between Exhibit A and the claimed invention is unclear. Exhibit A does not contain any information that any of the adenovirus described therein where part of Applicants' conception of the claimed invention. The experiments shown by Exhibit A appear to be directed to elucidation of the function of ADP, rather than its use. Furthermore, Exhibit A contains no information on the nature of the mutation in dl734 and dl753 that lead to ADP overexpression. Tollefson (Virol. 220: 152-162, 1996) shows that the deletion at least in dl753 removes coding sequence for the 10.4K protein, and does not involve removal of any splice sites. No evidence has been provided relating either dl734 or dl753 to conception of the claimed invention. The specification does not describe either adenovirus, an absence which is noteworthy given that a publication describing dl753 establish a statutory bar to many of the claims. Also, while the specification describes deletion of coding sequence for the 10.4K protein in the context of the claimed invention in order to increase immune response to transfected neoplastic cells, it does not teach that inactivation of E3 coding regions would lead to overexpression of ADP. The only type of E3 mutation taught in the specification for ADP overexpression is the removal of splice sites. Thus, based upon the instant specification, one of skill in the art would not have expected dl753 to overexpress ADP.

No evidence has been provided that Applicant had conceived of an adenovirus that would overexpress ADP, as opposed to an adenovirus which would simply express ADP, or the genomic structures (the means) that would lead to such overexpression prior to the effective filing date of the patents. As indicated on pages 7 and 8 of the declaration, it was not until after 4/18/97 that Applicants were aware that KD1 "overexpresses ADP", which is after the effective dates of Henderson and Little. While it is clear from the evidence of record that KD1 does overexpress ADP at early stages of infection, it is only in hindsight relative to the effective dates of the patents that one would have been aware that it read on the claimed invention. Thus, the evidence presented in the Declaration suggests that the claimed invention was conceived after the effective date of the patents as a result of characterization of KD1 and subsequent vectors.

Double Patenting

Claims 1, 2, 4, and 10-13 remain rejected and claims 33-55 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of copending Application No. 09/956,335. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims embrace the embodiment represented in the claims of the '335 application, wherein the adenovirus vector is replication restricted to cells expressing a telomerase.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant's acknowledgment of the provisional rejection and intent to address it should the co-pending claims issue are noted.

Allowable Subject Matter

Claims 5 and 15 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claims 14 and 24 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, second paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims.

Conclusion

Applicant's amendment (including the new information provided in the declaration) necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Certain papers related to this application may be submitted to Art Unit 1632 by facsimile transmission. The FAX numbers are (703) 308-4242 or (703) 305-3014 for any type of communication. In addition, FAX numbers for a computer server system using RightFAX are also available for communications before final rejection, (703) 872-9306, and for communications after final rejection, (703) 872-9307, which will generate a return receipt. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe whose telephone number is (703) 308-7310. The examiner can normally be reached on Monday through Friday from 8 AM to 4 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Scott D. Priebe

Scott D. Priebe, Ph.D.
Primary Examiner
Technology Center 1600
Art Unit 1632